

(19)  **Canadian
Intellectual Property
Office**

An Agency of
Industry Canada

**Office de la Propriété
Intellectuelle
du Canada**

Un organisme
d'Industrie Canada

(11) **CA 2 542 434** (13) **A1**
(40) 06.05.2005
(43) 06.05.2005

(12)

(21) **2 542 434**

(22) **18.10.2004**

(51) Int. Cl.:

A61K 31/27 (2006 01)

A61K 31/4453 (2006 01)

A61P 25/06 (2006 01)

A61K 31/44 (2006 01)

A61P 25/02 (2006 01)

(85) **12.04.2006**

(86) **PCT/EP04/011718**

(87) **WO05/039576**

(30) 103 49 729.3 DE 23.10.2003
103 59 335.7 DE 16.12.2003

(71) VIATRIS GMBH & CO. KG,
Benzstrasse 1
61352, BAD HOMBURG, XX (DE).

(72) SZELENYI, ISTVAN (DE).
BRUNE, KAY (DE).
LOCHER, MATHIAS (DE).
HERMANN, ROBERT (DE).

(74) MARKS & CLERK

(54) ASSOCIATIONS D'OUVREURS DES CANAUX POTASSIQUES ET D'INHIBITEURS DES CANAUX SODIQUES
OU DE PRINCIPES ACTIFS INFLUENCANT LES CANAUX SODIQUES UTILISEES POUR TRAITER DES
ETATS DOULOUREUX

(54) COMBINATIONS OF POTASSIUM CHANNEL OPENERS AND SODIUM CHANNEL INHIBITORS OR ACTIVE
SUBSTANCES INFLUENCING SODIUM CHANNELS IN ORDER TO TREAT PAINFUL CONDITIONS

(57)

The invention relates to medicament combinations
of potassium channel openers and sodium channel
inhibitors in order to treat painful conditions
associated with high muscle tone.



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2542434 A1 2005/05/06

(21) **2 542 434**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2004/10/18
(87) Date publication PCT/PCT Publication Date: 2005/05/06
(85) Entrée phase nationale/National Entry: 2006/04/12
(86) N° demande PCT/PCT Application No.: EP 2004/011718
(87) N° publication PCT/PCT Publication No.: 2005/039576
(30) Priorités/Priorities: 2003/10/23 (DE103 49 729.3);
2003/12/16 (DE103 59 335.7)

(51) Cl.Int./Int.Cl. *A61K 31/44* (2006.01),
A61K 31/27 (2006.01), *A61K 31/4453* (2006.01),
A61P 25/02 (2006.01), *A61P 25/06* (2006.01)

(71) Demandeur/Applicant:
VIATRIS GMBH & CO. KG, DE

(72) Inventeurs/Inventors:
HERMANN, ROBERT, DE;
LOCHER, MATHIAS, DE;
SZELENYI, ISTVAN, DE;
BRUNE, KAY, DE

(74) Agent: MARKS & CLERK

(54) Titre : ASSOCIATIONS D'OUVREURS DES CANAUX POTASSIQUES ET D'INHIBITEURS DES CANAUX
SODIQUES OU DE PRINCIPES ACTIFS INFLUENCANT LES CANAUX SODIQUES UTILISEES POUR TRAITER
DES ETATS DOULOUREUX
(54) Title: COMBINATIONS OF POTASSIUM CHANNEL OPENERS AND SODIUM CHANNEL INHIBITORS OR ACTIVE
SUBSTANCES INFLUENCING SODIUM CHANNELS IN ORDER TO TREAT PAINFUL CONDITIONS

(57) **Abstré/Abstract:**

The invention relates to medicament combinations of potassium channel openers and sodium channel inhibitors in order to treat painful conditions associated with high muscle tone.

Canada

<http://opic.gc.ca> • Ottawa-Hull K1A 0C9 • <http://cipo.gc.ca>

OPIC • CIPO 191

OPIC



CIPO

Abstract

The invention relates to pharmaceutical combinations of potassium channel openers and sodium channel inhibitors for the treatment of painful conditions associated with elevated muscle tone.

Combinations of potassium channel openers and sodium channel inhibitors or active substances influencing sodium channels in order to treat painful conditions

- 5 The invention relates to pharmaceutical combinations of potassium channel openers and sodium channel inhibitors for the treatment of painful conditions associated with elevated muscle tone.
- 10 A number of diverse painful disorders is associated with elevated skeletal muscle tone. In some cases, the development of pain is initiated by inflammations in a joint, consequently a painful posture results and is often accompanied by painful muscle spasms. The therapy
- 15 of such disorders includes, for example, benzodiazepines, but they entail a marked potential for addiction and are thus of limited use. Treatment of the underlying disorder, e.g. of the rheumatoid inflammation, often does not result in appropriate
- 20 satisfactory therapeutic successes. Additional administration of analgesics and/or skeletal muscle relaxants is therefore often indicated.

Centrally acting muscle relaxants are employed in

25 clinical practice in order to alleviate abnormally elevated muscle tone in patients suffering from painful muscle spasms and/or rigidity associated with rheumatoid disorders or spasms connected with neurological disorders. A number of corresponding

30 active substances is available commercially, but their clinical efficacy is often doubtful or is limited by unwanted side effects.

One class of such active substances are the Na⁺ channel

35 inhibiting substances. There are indications that they are able to relax an elevated muscle tone. It has been possible to show that propofol in clinically relevant concentrations has a distinct inhibitory effect on the sodium channels of the sarcolemma. This mechanism might

- 2 -

contribute to reducing muscle tone (Haeseler et al., Anesth Analg 2001; 92:1192-8). It has likewise been possible to show that inhibition of Na⁺ channels brings about inhibition of neurotransmitter release from the presynaptic ends (Obrenovitch, Int Rev Neurobiol 1997; 40:109-35). The neuroprotective active ingredient riluzole is a sodium channel inhibitor and an anti-excitotoxic substance employed for the treatment of amyotrophic lateral sclerosis. Kennel et al. (J Neurol Sci 2000; 180:55-61) have recently been able to show that riluzole significantly delays the onset of paralysis and the progression of functional parameters in conjunction with muscle strength in the mouse model of motor neurone disease. Metilexine, an antiarrhythmic and antimyotonic substance, blocks the sodium channels of skeletal muscles (Duranti et al., Eur J Med Chem 2000; 35:147-56) and solves skeletal muscle hyperexcitability in the mouse model of hereditary myotonia (De Luca et al., J Pharmacol Exp Ther 1997; 282:93-100). The important function of skeletal muscle sodium channels in maintaining normal tone is by the fact that it has been possible to show an association between mutations in the gene for the α subunit of the voltage-induced Na⁺ channel (SCN4A) with hereditary non-dystrophic myotonia. It is of interest that the myotonia dramatically resolved on administration of the Na⁺ channel-inhibiting substance flecainide (Rosenfeld et al., Ann Neurol 1997; 42:811-4).

Tolperisone is a centrally acting muscle relaxant with a relatively good clinical tolerability. Relatively few publications to date have dealt with the mechanism of action of tolperisone-like compounds. Tolperisone depresses production of the spinal segment reflex and effectively reduces the conduction, induced by C fibers, of afferent nerves both *in vivo* and *in vitro* (Farkas et al., Neurobiology 1997; 5:57-58). Compared with lidocaine, a local anesthetic, the substance has a smaller blocking effect on conduction of A fibers. Its

- 3 -

most characteristic effect is strong inhibition of mono- and polysynaptic spinal reflexes (Farkas et al., Neurobiology 1997; 5:57-58, Kocsis et al., Acta Pharm Hung 2002; 72(1):49-61, Okada et al., Jpn J Pharmacol 2001; 86:134-136). Ono et al. (J Pharmacobio Dynam 1984; 7:171-178) were able to show that tolperisone shows an effect similar to a local anesthetic ("membrane-stabilizing") both in motor neurones and in primary afferents *in vivo*, and on the peripheral nerves of rats *in vitro*. The effect of tolperisone appears to be similar to that of lidocaine, which is known to act as an inhibitor of voltage-gated sodium channels (Strathmann 2002, www.ifap-index.de/bda/hausarzt/19-2002/64-83.pdf). It has been possible to show that tolperisone, similar to lidocaine, blocks tetrodotoxin (TTX)-sensitive and TTX-resistant currents and thus suggests an inhibitory effect on both types of voltage-gated sodium channels (Bastigkeit, MMW-Forsch Med 2000; 142:50-51, Farkas et al., 2000, <http://www.asso.univ-paris5.fr/ewcbr/Francais/EWCBR2000/Abstracts/ABST126.htm>; Kocsis et al., Acta Pharm Hung 2002; 72(1):49-61). It is probable in this connection that the mechanism of action of tolperisone is somewhat different from that of lidocaine. There are moreover indications that tolperisone reduces sodium permeability. This effect might be responsible for the excitability-reducing effect of tolperisone and thus for the antispastic effect which it has been possible to document in clinical observations (Hinck and Koppenhofer, Gen Physiol Biophys 2001; 20:413-29). In addition, it has been possible to show in voltage clamp experiments on snail neurones that tolperisone and its analogs inhibit voltage-gated calcium currents (Novalies-Li et al., Eur J Pharmacol 1989; 168:299-305). Tolperisone analogs such as eperisone and silperisone showed a similar behavior in electrophysiological experiments. Thus, it was possible to show for example that silperisone reduces sodium permeability (During and Koppenhofer, Gen Physiol

- 4 -

Biophys 2001; 20:157-73). It can be concluded from this that these substances might reduce spastic skeletal muscle tone.

5 It was further possible to show in clinical studies that these substances can alleviate painful spasms associated with neurological or rheumatoid disorders. It has been reported that tolperisone is employed effectively in the treatment of muscle spasms (Pratzel
10 et al., Pain 1996; 67:417-25). Some derivatives of tolperisone, e.g. eperisone, likewise showed efficacy in the treatment of painful muscle spasms (Bose, Methods Find Exp Clin Pharmacol 1999; 21:209-13). Under certain pathological conditions, neurones are in a
15 state of continuous depolarization so that their sodium channels respond more sensitively to the inhibitory effect of certain substances. This makes it possible to alleviate muscle spasms and pain with a favorable profile of side effects. Recent data indicate that
20 tolperisone and its analogs have selective inhibitory effects on voltage-gated sodium channels. This mechanism might be responsible for their spinal reflex-suppressing and muscle-relaxant effect. In addition, this property might bring about the analgesic effect
25 which, on the basis of the small differences observed, might be free of side effects in contrast to lidocaine.

A further class of muscle-relaxant substances are the potassium channel openers. These include for example
30 flupirtine from a class of triaminopyridines, which is employed as non-opioid analgesic with muscle-relaxant properties. It has been possible to show that flupirtine reduces skeletal muscle tone when employed in doses comparable to those for the antinociceptive
35 effect (Nickel et al., Arzn Forsch/Drug Res 1990a; 40:909-11).

Since diazepam and other benzodiazepines are frequently employed as muscle relaxants, it was obvious to compare the pharmacodynamic properties of flupirtine with those

- 5 -

of the benzodiazepines. In receptor-binding studies, no affinity was detected for specific $[^3H]$ flunitrazepam up to a concentration of 10 $\mu\text{mol/l}$ (Nickel et al., *Arzn Forsch/Drug Res* 1990b; 40:905-908). In relation to the changes in the EEG, distinct differences were detectable in the profiles induced by flupirtine and benzodiazepines (Nickel, *Postgrad Med J* 1987; 63:19-28). Electrophysiological investigations showed that flupirtine influences GABAergic conduction by potentiating the effect of GABA (Weiser et al., *Arch Pharmacol* 1992; 346(Suppl.):R22). Data from *in vitro* and *in vivo* analyses suggests that flupirtine behaves like a functional N-methyl-D-aspartate (NMDA) antagonist. It might be concluded from this that this mechanism might be involved in the muscle-relaxant effect of flupirtine (Schwarz et al., *Neuroreport* 1994; 5:1981-4). Recent investigations indicate that flupirtine activates voltage-independent potassium channels (Kornhuber et al., *J Neural Transm* 1999; 106:857-67). This potassium channel-opening effect of flupirtine might be responsible for its analgesic and skeletal muscle-relaxant effect.

The described prior art clearly shows that although there is a number of substances employed for treating painful conditions with elevated muscle tone, there are frequently limitations to this due to unwanted side effects. Thus, for example, flupirtine in higher dosage shows neurotoxic effects such as drowsiness, coordination impairment. Tolperisone shows no serious unwanted side effects, but its efficacy and duration of action in muscle relaxation are unsatisfactory, possibly owing to the relatively low bioavailability and the short half-life in humans (Ito et al., *Arch Int Pharmacodyn Ther* 1985; 275:105-22, Matsunaga et al., *Jpn J Pharmacol* 1997; 73:215-20).

It is therefore an object of this invention to provide a medicament for the treatment of painful conditions

- 6 -

associated with elevated muscle tone, which shows fewer side effects with a comparable effect or which has an increased efficacy at the same dose.

- 5 It has been possible to bring this about according to the invention by the novel combination of a potassium channel opener and of a sodium channel inhibitor. It has been possible to show that the muscle-relaxant effect is increased by the combination of sodium
- 10 channel inhibiting or influencing active substances and potassium channel openers. Examples of Na^+ channel inhibiting or influencing substances which can be employed are: tolperisone and its analogs eperisone and silperisone, riluzole,
- 15 propafenone, lidocaine, flecainide, metixene, and their pharmaceutically usable salts. Flupirtine is to be mentioned as example of potassium channel opener.

- 20 The combination of tolperisone or its analogs and flupirtine or its pharmaceutically usable salts is particularly preferred in this connection. The combination of the invention makes the treatment of painful conditions associated with elevated muscle tone
- 25 more effective and safe. The combination of sodium channel inhibiting or influencing substances and potassium channel openers such as flupirtine leads to an increased therapeutic effect or improved tolerability. It has been possible to show for example
- 30 that the muscle-relaxant effect of flupirtine can be enhanced by Na channel inhibiting or influencing active substances such as tolperisone, and vice versa. However, particularly surprising and unexpected for the skilled worker is the effect that the skeletal muscle-
- 35 relaxant effect of flupirtine is enhanced super-additively by tolperisone, and vice versa. In contrast thereto, the neurotoxicity of flupirtine is not enhanced by tolperisone.

The combination of the two substances can be employed

- 7 -

for the treatment of painful conditions associated with disorders of skeletal muscles which are associated with hypermyotonia and restricted mobility, especially those caused by injuries to the spinal cord, osteoporosis, arthritis and stiffening/spastic conditions. It is additionally effective for painful conditions caused by the following: lumbar neurolathyrism, arthritis, disorders of the peripheral circulatory system, menopausal muscular and vascular symptoms, trismus, myogenic headache, rheumatic disorders associated with muscle hypertonia, spasms, pain, inflammatory symptoms and restricted mobility, multiple sclerosis, and in the postoperative treatment of trauma patients, and for the treatment of lower spastic paraparesis syndrome: lower paraspasm, transverse myelitis, multiple sclerosis, hereditary inferior spastic paraplegia (Stuempel's paraplegia), impairments of the spinal blood circulation, cerebral paralysis with lower spastic paresis, tetraparesis associated with cervical myelopathy, vertebral dysplasia, tension headache and cervical brachialgia.

Pharmacological examples

- 25 1: *Muscle-relaxant effect on reserpine-induced muscle rigidity in rats*

Results

- 30 Both flupirtine and tolperisone reduce dose-dependently the reserpine-induced skeletal muscle rigidity in conscious rats. The intraperitoneal (i.p.) ED₅₀ for flupirtine was 6.45 mg/kg. The ED₅₀ for tolperisone was 32.4 mg/kg i.p.
- 35 The results in tables 1 and 2 show clearly that there is a surprising superadditive enhancement of the skeletal muscle-relaxant effect of flupirtine by tolperisone and vice versa.

- 8 -

Table 1. Effect of flupirtine administered intraperitoneally in combination with tolperisone on reserpine-induced skeletal muscle rigidity in conscious rats

5

Treatment		Muscle relaxation (%)	
		calculated	measured
Flupirtine 5 mg/kg	+ tolperisone 12.5 mg/kg	52.2	71.1*
Flupirtine 5 mg/kg	+ tolperisone 25 mg/kg	75.4	90.7*
Flupirtine 5 mg/kg	+ tolperisone 50 mg/kg	121.0	163.2*

Table 2. Effect of tolperisone administered intraperitoneally in combination with flupirtine on reserpine-induced skeletal muscle rigidity in conscious rats

10

Treatment		Muscle relaxation (%)	
		calculated	measured
Tolperisone 25 mg/kg	+ flupirtine 1 mg/kg	44.7	60.2*
Tolperisone 25 mg/kg	+ flupirtine 3 mg/kg	60.0	81.4*
Tolperisone 25 mg/kg	+ flupirtine 5 mg/kg	75.4	92.1*

Description of the experiment

- 15 Male Sprague-Dawley rats weighing 200-220 g were kept in two groups under standard conditions (temperature 22°C, humidity 40-60%) without food and water restriction. Illumination took place from 6.00-18.00 h. The experiments were approved by the local animal health committee responsible for the protection and proper use of experimental animals.
- 20

- 9 -

The experimental design has already been described in detail (Nickel et al., *Arzn Forsch/Drug Res* 1997; 47:1081-6). Described briefly, the muscle rigidity was measured on skeletal muscles by successive measurement of the resistance of the flexor and extensor muscles which have contrary effects in the joint during stretching and flexion of the foot. The differences in pressure generated by the foot movement were continuously recorded. The signals were analyzed by means of a PC program which calculated the values for the resistance of flexor and extensor in the foot over 10 min periods.

The active substances were made up fresh each day and administered i.p. in various doses simultaneously 16 h after the reserpine injection (2 mg/kg, intraperitoneal).

Statistical analysis of the differences between the calculated and measured values was carried out by one-way ANOVA. (*) identifies the significant level $p < 0.01$.

2: Investigations on the skeletal muscle tone of mice in the so-called inclined screen test

Results

It was possible convincingly to verify the surprising results of example 1 in an experiment on mice. Both flupirtine and tolperisone reduce the skeletal muscle tone dose-dependently in conscious mice and thus provide information on their muscle-relaxant effect. The intraperitoneal (i.p.) ED_{50} for flupirtine is 10.8 mg/kg. The ED_{50} for tolperisone is 51.0 mg/kg i.p. The results in tables 3 and 4 show clearly that on simultaneous i.p. administration of various doses of flupirtine and tolperisone the skeletal muscle-relaxant effect of flupirtine is enhanced superadditively by tolperisone and vice versa.

- 10 -

Table 3. Effect of flupirtine administered intra-peritoneally in combination with tolperisone on the skeletal muscle tone of conscious mice.

Treatment		Number of animals falling from incline in %	
		calculated	measured
Flupirtine 1 mg/kg	+ tolperisone 12.5 mg/kg	14	54*
Flupirtine 1 mg/kg	+ tolperisone 25 mg/kg	28	62*
Flupirtine 1 mg/kg	+ tolperisone 50 mg/kg	54	75*

5

Table 4. Effect of tolperisone administered intra-peritoneally in combination with flupirtine on the skeletal muscle tone of conscious mice.

Treatment		Number of animals falling from incline in %	
		calculated	measured
Tolperisone 25 mg/kg	+ flupirtine 1 mg/kg	28	50*
Tolperisone 25 mg/kg	+ flupirtine 3 mg/kg	37	60*
Tolperisone 25 mg/kg	+ flupirtine 5 mg/kg	46	70*

10

Description of the experiment

NMRI mice weighing 22-24 g were kept in four groups under standard conditions (temperature 22°C, humidity 40-60%) without food and water restriction. Illumination took place from 6.00-18.00 h. All the experiments were approved by the local animal health committee responsible for the protection and proper use of experimental animals.

The pharmacological model employed to make it possible

20

- 11 -

to predict the muscle-relaxant properties was the so-called 30 degrees inclined screen test (Simiand et al., Arch Int Pharmacodyn Ther 1989; 297:272-85). The inclined screen consists of a wooden frame with a wire mesh screen which can be inclined at any angle (in this case: 80°). The lower part of the screen is 15 cm above the table. The animals are placed on the inclined screen, and their ability to stay on the inclined screen is observed over a period of 30 s. The number of animals falling off the screen is counted and the proportion of them in the total number in each group is calculated.

The active substances were made up fresh each day and administered simultaneously i.p. in various doses 1 h before starting the experiments to analyze the skeletal muscle tone.

Statistical analysis of the differences between the calculated and measured values were carried out by one-way ANOVA. (*) indicates the significant level $p < 0.01$.

3: Possible neurotoxic effects of the substances, measured in the rotating rod test on rats

Results

Centrally acting substances may have neurotoxic side effects which might restrict their therapeutic use. The results in tables 5 and 6 show clearly that the combination of flupirtine and tolperisone has an additive effect on motor coordination. No superadditive effect can be observed, i.e. the flupirtine + tolperisone combination does not lead to an increase in unwanted central nervous effects.

- 12 -

Table 5. Effect of flupirtine administered intra-peritoneally in combination with tolperisone on motor coordination of rats by means of the rotating rod.

Treatment		Number of animals falling from incline in %	
		calculated	measured
Flupirtine 1 mg/kg	+ tolperisone 12.5 mg/kg	38	42
Flupirtine 1 mg/kg	+ tolperisone 25 mg/kg	50	49
Flupirtine 1 mg/kg	+ tolperisone 50 mg/kg	70	67

5

Table 6. Effect of tolperisone administered intra-peritoneally in combination with flupirtine on motor coordination of rats by means of the rotating rod.

Treatment		Number of animals falling from incline in %	
		calculated	measured
Tolperisone 25 mg/kg	+ flupirtine 1 mg/kg	49	50
Tolperisone 25 mg/kg	+ flupirtine 3 mg/kg	57	50
Tolperisone 25 mg/kg	+ flupirtine 5 mg/kg	66	67

10

Description of the experiment

- Male Sprague-Dawley rats weighing 200-220 g were kept in two groups under standard conditions (temperature 22°C, humidity 40-60%) without food and water restriction. Illumination took place from 6.00-18.00 h. The experiments were approved by the local animal health committee responsible for the protection and proper use of experimental animals.
- The motor coordination and balance of the animals was

- 13 -

analyzed in the so-called rotating rod test (Jones and Roberts, J Pharm Pharmacol 1968; 20:302-304). The animals are placed on a rotating rod (diameter 10 cm; length 60 cm; 5 rpm) and the number of animals
5 remaining on the rod after a period of 2 minutes is counted. The active substances were made up fresh each day and administered simultaneously in various doses intraperitoneally 30 min before starting the experiments.

10

The described experiments clearly show the effects of the flupirtine/tolperisone combination. It is possible to infer from the comparable mechanisms of actions of the potassium channel openers and sodium channel
15 inhibiting or influencing substances that other combinations of substances of these classes of substances will have the same positive effect.

The combinations of Na⁺ channel inhibiting or
20 influencing active substances and potassium channel openers and their pharmaceutically usable salts can be administered in all oral, enteral, rectal, lingual, intravenous, intramuscular, intraperitoneal, transdermal, subcutaneous or intracutaneous dosage
25 forms. Preferred oral dosage forms are, for example, tablets, film-coated tablets, sugar-coated tablets, hard capsules, soft capsules, chewable tablets, suckable tablets, syrup, preparations with controlled release (e.g. dual formulation, sustained release
30 formulation), pellets, chewable tablets or soluble granules. Examples of further suitable dosage forms are: solutions for injection, suspensions, suppositories, creams, ointments, gels, transdermal administration forms, sub- or intracutaneous implants.

35

The substances can be administered simultaneously, successively or in a fixed combination. They can be administered together in one dosage form or in two dosage forms which may be identical or different. They

- 14 -

can be administered simultaneously or successively, either in quick succession or with larger time intervals, e.g. flupirtine in the evening and tolperisone in the morning.

- 5 The active substances can be administered between 1 and 8 times a day in sufficient quantity to achieve the desired effect. The active substances are preferably administered one to four times a day.

- 10 The daily dose should comply with the authorized amount of the respective substances employed in the combination. This is for the preferred combination for example between 150 and 450 mg/day tolperisone for adults, flupirtine 100-800 mg/day, preferably between 200 and 400 mg/day.

- 15 -

Claims

1. The use of potassium channel openers in combination with sodium channel inhibiting or
5 influencing substances or their therapeutically employable salts for the treatment of painful conditions associated with elevated muscle tone.
2. The use as claimed in claim 1, characterized in
10 that flupirtine or its pharmaceutically usable salts are employed as potassium channel openers.
3. The use as claimed in claim 1, characterized in
15 that tolperisone or its analogs eperisone or silperisone, or riluzole, propafenone, lidocaine, flecainide, metixene, or their pharmaceutically usable salts are employed as sodium channel inhibiting or influencing substances.
- 20 4. The use as claimed in claim 1, characterized in that tolperisone or its analogs eperisone or silperisone, or their pharmaceutically usable salts are employed as sodium channel inhibiting or influencing substances.
- 25 5. The use of flupirtine in combination with tolperisone or its analogs such as eperisone or silperisone, or their pharmaceutically usable salts for the treatment of painful conditions
30 associated with elevated muscle tone.
6. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically
35 employable salts as claimed in claim 1 for the treatment of neuralgias.
7. The use of potassium channel openers in

- 16 -

combination with sodium channel inhibiting or influencing substances and their therapeutically employable salts as claimed in claim 1 for the treatment of arthritis and arthroses.

5

8. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically employable salts as claimed in claim 1 for the treatment of chronic or episodic tension headache.

10

9. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically employable salts as claimed in claim 1 for the treatment of lower spastic paraparesis syndrome (e.g. lower paraspasm, transverse myelitis, multiple sclerosis, hereditary inferior spastic paraplegia (Stuempel's paraplegia), impairments of the spinal blood circulation, cerebral paralysis with lower spastic paresis).

15

20

10. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically employable salts as claimed in claim 1 for the treatment of tetraparesis associated with cervical myelopathy, cervical brachialgia or vertebral dysplasia.

25

30

11. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically employable salts as claimed in claim 1 for the treatment of Parkinson's disease.

35

12. The use of potassium channel openers in combination with sodium channel inhibiting or influencing substances and their therapeutically

- 17 -

employable salts for producing a medicament for oral, rectal, intravenous, transdermal, sub- or intracutaneous administration for the treatment of painful conditions associated with elevated muscle tone.